

## Research report

# Effects of heavy particle irradiation and diet on amphetamine- and lithium chloride-induced taste avoidance learning in rats

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**Abstract**

Rats were maintained on diets containing either 2% blueberry or strawberry extract or a control diet for 8 weeks prior to being exposed to 1.5 Gy of <sup>56</sup>Fe particles in the Alternating Gradient Synchrotron at Brookhaven National Laboratory. Three days following irradiation, the rats were tested for the effects of irradiation on the acquisition of an amphetamine- or lithium chloride-induced (LiCl) conditioned taste avoidance (CTA). The rats maintained on the control diet failed to show the acquisition of a CTA following injection of amphetamine. In contrast, the rats maintained on antioxidant diets (strawberry or blueberry extract) continued to show the development of an amphetamine-induced CTA following exposure to <sup>56</sup>Fe particles. Neither irradiation nor diet had an effect on the acquisition of a LiCl-induced CTA. The results are interpreted as indicating that oxidative stress following exposure to <sup>56</sup>Fe particles may be responsible for the disruption of the dopamine-mediated amphetamine-induced CTA in rats fed control diets; and that a reduction in oxidative stress produced by the antioxidant diets functions to reinstate the dopamine-mediated CTA. The failure of either irradiation or diet to influence LiCl-induced responding suggests that oxidative stress may not be involved in CTA learning following injection of LiCl.

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*Theme:* Neural basis of behavior*Topic:* Learning and memory: pharmacology*Keywords:* <sup>56</sup>Fe particle; Antioxidant; Oxidative stress; Aging**1. Introduction**

Exposing a rat to heavy particles such as <sup>56</sup>Fe (a ground-based model for exposure to cosmic rays) produces neurochemical and behavioral changes which approximate those seen in the aged organism. Among various neurochemical and behavioral endpoints, aging is characterized by reductions in: (1) potassium enhanced dopamine release from the striatum; (2) upper body strength, measured by the capacity of a rat to maintain its position on a wire; and (3) cognitive performance, measured using the Morris water maze [1,7]. Exposing rats to non-lethal levels of <sup>56</sup>Fe particles (1.0–1.5 Gy, 1 GeV/n) produces equivalent changes in dopamine release and in motor behavior [4,5]. Similarly, exposure to <sup>56</sup>Fe particles produces deficits in

performance in the Morris water maze [19] and, in addition, in amphetamine-induced conditioned taste avoidance (CTA) learning, which depends upon the integrity of the dopaminergic system, but not in lithium chloride (LiCl)-induced CTA learning which is independent of the dopaminergic system [16,17].

Current theories suggest that free radical production and oxidative stress are important factors in the aging process [2,3]. Similarly, exposure to ionizing radiation causes the production of reactive oxygen species and oxidative stress [18,20]. Research by Joseph and colleagues [1,7,8] has shown that maintaining rats on diets containing dietary antioxidants can prevent the occurrence of the neurochemical and behavioral changes that characterize the aged organism. Given the similarities between the normal aging process and the effects of exposure to heavy particles [6], there is the possibility that dietary antioxidants will be equally effective in preventing the behavioral changes produced by exposure to <sup>56</sup>Fe particles. As such, it is

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possible that dietary antioxidants may be able to serve as effective countermeasures to the effects of exposure to cosmic rays.

The present experiment was designed to examine two aspects of the involvement of free radicals and oxidative stress in the acquisition of a CTA produced by treatment with amphetamine or LiCl and in the effects of exposure to heavy particles on this behavior. First, previous research has shown that exposure to  $^{56}\text{Fe}$  particles attenuates the acquisition of an amphetamine-induced CTA [6]. If irradiation affects behavior by producing free radicals and oxidative stress, then antioxidant diets may be expected to prevent the attenuation of an amphetamine-induced CTA by exposure to  $^{56}\text{Fe}$  particles.

A second issue concerns the possibility that free radicals and oxidative stress are directly involved in the acquisition of a CTA produced by treatment with amphetamine or LiCl. Injection of the free radical generator sodium nitroprusside and the spin-trapping agent *N*-tert-butyl-L-phenyl nitron produce a CTA that can be attenuated by pretreating subjects with the nitric oxide synthase inhibitor nitro-arginine [11]. However, there is not unequivocal support for possible involvement of free radicals in the acquisition of an amphetamine- or LiCl-induced CTA. Rabin found that pretreating rats with the nitric oxide synthase inhibitor nitro-arginine (10–20 mg/kg) did not affect the acquisition of a radiation-induced CTA [11]. In contrast, Wegener et al. [22] reported that higher doses of nitro-arginine (50–500 mg/kg) were effective in attenuating an LiCl-induced avoidance, despite the fact that the acquisition of both LiCl- and radiation-induced taste avoidances involves similar mechanisms [13,15].

Previous research has shown that exposing rats to  $^{56}\text{Fe}$  particles results in the acquisition of a significantly attenuated CTA following injection of amphetamine, but has no effect on the acquisition of a LiCl-induced CTA [16,17]. The present experiment was designed to evaluate the role of free radicals and oxidative stress in the heavy particle-induced disruption of an amphetamine-induced CTA and in the acquisition of an amphetamine- or LiCl-induced CTA. First, if oxidative stress produced by exposure to  $^{56}\text{Fe}$  particles is involved in the attenuation of an amphetamine-induced CTA, then rats maintained on an antioxidant diet should continue to show an amphetamine-induced CTA following irradiation. Second, to the extent that oxidative stress and free radical production is directly involved in the acquisition of amphetamine- or LiCl-induced CTA learning, then the antioxidant diets should disrupt the taste avoidance learning in non-irradiated rats.

## 2. Materials and methods

### 2.1. Subjects

The subjects were 96 male Sprague–Dawley rats weigh-

ing 175–200 g at the start of the experiment. They were housed in AAALAC (American Association for Accreditation of Laboratory Animal Care)-accredited animal facilities at Brookhaven National Laboratory (BNL). The rats were maintained on a 12:12 h light–dark cycle. Food and water were continuously available except as required for CTA training.

The rats were divided into twelve groups. First, 2 months prior to irradiation, rats were placed on diets containing either 2% blueberry or strawberry extract or a control diet, with 32 rats fed each diet. Then, half the rats in each diet condition were irradiated while the remaining rats served as non-irradiated controls. Finally, each of the groups was further subdivided by treatment compound (amphetamine/LiCl). Thus, each of the 12 experimental conditions had a sample size of eight rats. All rats were maintained on their respective diets through the conclusion of the CTA testing.

A saline injected control group was not included in the present experiment because previous experiments [16,17] had already established that exposure to  $^{56}\text{Fe}$  particles attenuated the acquisition of an amphetamine-induced CTA, but had no effect on the acquisition of an LiCl-induced CTA. In addition, previous research [Rabin, unpublished] had shown that exposure to heavy particles did not affect the normal increase in test day sucrose intake by rats given an injection of saline on the conditioning day. As such only two control groups were used: (1) a control diet to provide a comparison group for the effects of the diets containing blueberry or strawberry extract; and (2) a non-irradiated group to provide a comparison for the rats exposed to  $^{56}\text{Fe}$  particles.

### 2.2. Diets

The diets were prepared by homogenizing blueberries or strawberries in water (1:1 or 2:1 w/v, respectively) for 3 min. The recovered homogenate was centrifuged at  $13\,000\times g$  for 15 min at 4 °C and the supernatant collected and lyophilized, as described previously [8]. Freeze dried extracts were shipped to Harlan Teklad (Madison, WI), where they were combined with the control diet (20 g/kg diet, 2% of the diet). The control diet was a modification of the NIH-31 diet and was similar to that used in a previous study in which beneficial effects on aging were found [24,25]. The amount of corn in the control diet was adjusted accordingly when the strawberry or blueberry extracts were added.

### 2.3. Radiation

Rats were irradiated with  $^{56}\text{Fe}$  particles using the Alternating Gradient Synchrotron at Brookhaven National Laboratory. For irradiation, rats were placed in a well-ventilated restraining tube which was placed perpendicular to the beam and positioned so that the head was in the

Table 1  
Sucrose intake (ml) in rats injected with amphetamine

	Conditioning day	Test day
<i>Non-irradiated rats</i>		
Control diet	15.62±0.65 <sup>a</sup>	8.25±0.84
Blueberry diet	14.88±1.43	9.00±1.43
Strawberry diet	15.88±0.90	10.50±0.91
<i>Irradiated rats</i>		
Control diet	12.75±1.10	11.25±0.53
Blueberry diet	11.62±0.73	8.88±0.77
Strawberry diet	11.65±0.68	6.25±0.88

<sup>a</sup> Mean±standard error of the mean (S.E.M.).

center of the beam, as determined by an X-ray film. The rats were exposed to 1.5 Gy of 1 GeV/n <sup>56</sup>Fe particles at a nominal dose rate of 1.0–1.5 Gy/min. Control rats were not exposed to the beam. The details of the beam and dosimetry have been provided by Zeitlin et al. [26].

#### 2.4. CTA training

A CTA was produced by placing rats on a 23.5-h water deprivation schedule for 7 days. On the conditioning day, which was 2–3 days after irradiation, the rat was presented with a single calibrated drinking tube containing a 10% sucrose solution for the 30-min drinking period, and intake measured. Immediately following the drinking period, half the rats in each radiation (irradiated, non-irradiated)/diet (control, blueberry, strawberry) condition were given an injection of amphetamine (3 mg/kg, ip) and the other half were given an injection of LiCl (2.2 mEq/kg, ip). The drugs were mixed with sterile water at a concentration of 3

mg/ml for amphetamine and 3.0 mEq/ml for the LiCl. On the test day, 24 h later, the rats were again presented with a calibrated drinking tube containing the 10% sucrose solution, and intake measured. A CTA is shown by a significant reduction in test day sucrose intake.

### 3. Results

The actual sucrose intake for the rats given amphetamine injections is presented in Table 1. As shown in Table 1, the conditioning day intake for the irradiated animals was significantly less than that of the non-irradiated animals ( $t(47)=2.97$ ,  $P<0.01$ ).

The effects of diet on the acquisition of an amphetamine-induced CTA in irradiated and non-irradiated rats is summarized in Fig. 1, in which test day intake is expressed as a percentage of conditioning day intake. For the animals maintained on the control diet, exposure to <sup>56</sup>Fe particles disrupted the acquisition of an amphetamine-induced CTA, such that injection of amphetamine did not produce a significant decrease in conditioning day sucrose intake. For the rats maintained on either the blueberry or strawberry diets, injection of amphetamine produced equivalent taste avoidances in both irradiated and non-irradiated rats.

Statistical analysis was performed by using an arcsin transformation to normalize the distributions. Significance was then tested with a two-way analysis of variance followed by post-hoc comparisons using Fisher's Protected  $t$ -tests. This analysis showed that neither the main effect for radiation ( $F[1,37]=3.00$ ,  $P>0.10$ ) nor the main effect

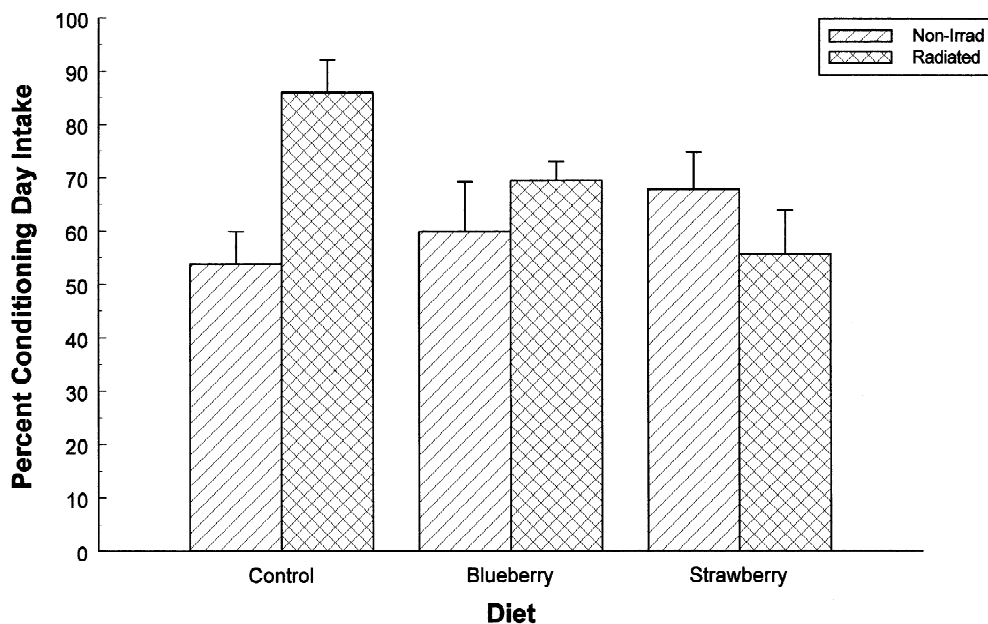


Fig. 1. Effects of control or antioxidant diets (blueberry or strawberry extract) on the acquisition of a CTA produced by injection of amphetamine (3 mg/kg, ip). Test day sucrose intake is presented as a percentage of conditioning day intake following the injection of amphetamine. Error bars indicate the standard error of the mean (S.E.M.).

for diet ( $F[2,37]=0.45$ ,  $P>0.10$ ) was significant. However, the radiation condition by diet interaction was significant. ( $F[2,37]=4.43$ ,  $P<0.02$ ), indicating that the effects of radiation on conditioning day sucrose intake varied as a function of diet. Post-hoc comparisons showed that the differences between the radiated and non-irradiated rats fed the control diet were significant ( $t=2.82$ ,  $P<0.01$ ). The differences between the irradiated and non-irradiated rats fed the blueberry ( $t=1.36$ ,  $P>0.05$ ) or the strawberry diet ( $t=1.37$ ,  $P>0.05$ ) were not significant. In addition, the radiated animals on the strawberry diet showed a significantly reduced test day sucrose intake compared to the irradiated rats maintained on a control diet ( $t=2.56$ ,  $P<0.05$ ).

For the rats in which LiCl was used to induce a CTA, the conditioning day intake of the non-irradiated rats was also significantly greater than the intake of the radiated rats (data not shown; ( $t(36)=6.91$ ,  $P<0.01$ ). The effects of diet on the acquisition of a LiCl CTA in radiated and non-irradiated rats is summarized in Fig. 2, in which test day intake is expressed as a percentage of conditioning day intake. Analysis of variance (using arcsin transformed scores) indicated that neither the main effect for radiation condition ( $F=2.27$ ,  $P>0.10$ ) nor the main effect for diet ( $F=0.004$ ,  $P>0.10$ ), nor the interaction between radiation condition and diet ( $F=0.08$ ,  $P>0.10$ ) were significant.

#### 4. Discussion

In terms of actual sucrose intake, the irradiated rats

showed a significantly reduced conditioning day intake compared to the non-irradiated rats. The factors that may have contributed to the decreased conditioning day intake are not certain. However, because there were no differences in conditioning day intake between the rats on the antioxidant diets and the rats on the control diet, it is unlikely that the decreased conditioning day sucrose intake influenced the test day intake.

Exposing rats maintained on the control diet to  $^{56}\text{Fe}$  particles attenuated, but did not eliminate, the CTA produced by injection of amphetamine CTA such that the decrease in sucrose intake was significantly less than that observed in non-irradiated animals. The results observed with the rats on a control diet are identical to the results that have been obtained in previous experiments [16,17]. In addition, the attenuation of an amphetamine-induced CTA by exposure to  $^{56}\text{Fe}$  particles is similar to the effects produced by injection of the  $\text{D}_2$  antagonist haloperidol [12]. Rabin and Hunt [12] reported that following injection of haloperidol (0.1–0.5 mg/kg) there was an attenuation of the amphetamine-induced reduction in test day sucrose intake, although there continued to be a reduction in sucrose intake compared to saline-injected controls. Because the acquisition of an amphetamine-induced CTA depends upon the integrity of the dopaminergic system [21,23], the present results are consistent with previous research which shows that exposure to  $^{56}\text{Fe}$  particles disrupts the functioning of the dopaminergic system and of dopamine-mediated behaviors [4,16,17].

When rats are maintained on diets containing antioxidants, blueberry or strawberry extract, this  $^{56}\text{Fe}$  par-

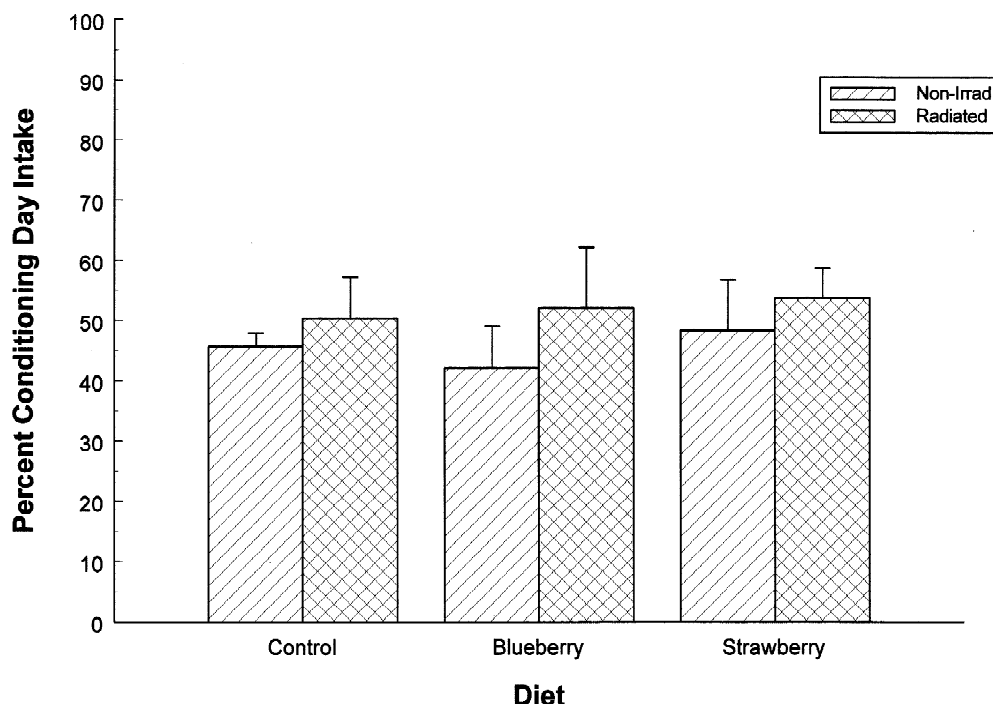


Fig. 2. Effects of control or antioxidant diets (blueberry or strawberry extract) on the acquisition of a CTA produced by injection of LiCl (2.2 mEq/kg). Test day sucrose intake is presented as a percentage of conditioning day intake following the injection of LiCl. Error bars indicate the S.E.M.

ticle-induced attenuation of an amphetamine-induced CTA is prevented and the irradiated and non-irradiated rats show the development of equivalent taste avoidances following injection of amphetamine. This observation would be consistent with the hypothesis that exposing rats to  $^{56}\text{Fe}$  particles normally produces increased oxidative stress which is responsible for the disruption of the dopamine-mediated behavior. In contrast to the results obtained with amphetamine, exposure to heavy particles had no effect on the acquisition of a LiCl-induced CTA. The results are consistent with those of preceding experiments, showing that  $^{56}\text{Fe}$  particle-induced oxidative stress has no effect on the acquisition of an LiCl-induced CTA which does not involve the mediation of the dopaminergic system [16,17].

For the non-irradiated rats, injected with either amphetamine or LiCl, there was no direct effect of diet on the acquisition of a CTA. These results indicate that oxidative stress or the production of reactive oxygen species are not factors in taste avoidance learning. The observation that oxidative stress by itself does not mediate the acquisition of a LiCl-induced CTA is consistent with the report that injecting rats with low doses of the nitric oxide synthase inhibitor nitro-arginine (10–20 mg/kg) does not disrupt the acquisition of a radiation-induced CTA [11]. However, the present results are not entirely consistent with the fact that pretreating rats with high doses of nitro-arginine (50–500 mg/kg) can attenuate the acquisition of an LiCl-induced CTA [22]. While it is possible that these differences reflect the different unconditioned stimuli, other research has shown that similar mechanisms underlie both radiation- and LiCl-induced CTAs [13,15]. Alternatively, because there are different sources and sites of action of reactive oxygen species [2], it is possible that the acquisition of an LiCl-induced CTA learning specifically involves nitric oxide whereas the dietary antioxidants affect different reactive oxygen species. As a result, the reduction of oxidative stress by dietary antioxidants in the present experiment may not have affected those species that mediate an LiCl-induced CTA.

Because antioxidant diets did not affect the acquisition of a CTA following injection of amphetamine in non-irradiated animals, the mechanisms underlying the effectiveness of the diets in reversing the  $^{56}\text{Fe}$  particle-induced attenuation of the amphetamine-induced CTA are a matter of speculation. Exposing rats to ionizing radiation is a source of oxidative stress and causes the release of reactive oxygen species [18,20]. Similarly, the amphetamine-induced release of dopamine may, under some conditions, also be a source of oxidative stress [9,10]. Under these conditions, it is possible that prior exposure to  $^{56}\text{Fe}$  particles produces latent inhibition which later interferes with the development of the dopamine-mediated amphetamine-induced CTA [16,17]. In this case the reestablishment of the amphetamine-induced CTA by the antioxidant diets may result from the possible elimination of the heavy particle-induced oxidative stress, and the related loss of latent inhibition. In contrast to amphetamine which can

produce a CTA by direct effects on the central nervous system [14], the LiCl-induced CTA is mediated by the effects of the compound on the peripheral system and depends upon the integrity of the area postrema. As such, it may be that the effects of exposure to  $^{56}\text{Fe}$  particles, which affect the CNS, were not similar enough to those produced by injection of LiCl to cause the development of latent inhibition.

As indicated above, exposing rats to heavy particles produces neurochemical and behavioral changes which are similar to those seen in aged organisms [4–6]. These changes can be minimized by maintaining rats on diets containing dietary antioxidants [1,7,8]. The present results showing a diet-induced reduction in the effects of oxidative stress following exposure to  $^{56}\text{Fe}$  particles provide additional support for the hypothesis that exposing an organism to  $^{56}\text{Fe}$  particles can produce accelerated aging [4,5]. In addition, because astronauts on long-duration missions outside the magnetosphere will be exposed to heavy particles, which are a constituent of cosmic rays, the present results suggest that providing astronauts diets containing dietary antioxidants may serve as effective countermeasures to prevent these neurochemical and behavioral changes.

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